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Arterial and Ventricular CSF Pharmacokinetics after Intrathecal Meperidine in Humans

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In order to investigate the mechanisms leading to respiratory depression after lumbar administration of opioids, plasma and ventricular CSF pharmacokinetics of intrathecal meperidine (1 mg · kg^{-1}) were studied in five head-injured patients undergoing surgery for lower limb fracture. Meperidine was detected both in the plasma (arterial catheter) and in the ventricular CSF (intracranial catheter) soon after intrathecal administration: 45 ± 17 min and 100 ± 14 min, respectively. The maximal plasma concentration was 341 ± 133 ng · ml^{-1}, whereas, in ventricular CSF, it was 64.5 ± 14.9 ng · ml^{-1}. The ventricular CSF-plasma ratio increased with time (r = 0.82) from 0.18 ± 0.04 at the first hour to 0.38 ± 0.1 at 16th hour. It is concluded that the putative risk of respiratory depression appears to be mainly related to the absorption into the systemic circulation and to redistribution back into CSF. (Key words: Anesthetics, opioid: meperidine. Anesthetic techniques, spinal: meperidine. Pharmacokinetics: meperidine.)

A DRUG IS CONSIDERED a local anesthetic if it can consistently and without toxicity block in a reversible manner both sensory and motor pathways. Intrathecal meperidine seems to fulfill these requirements.[1,2] Initially used in animals in 1978,[3] it later appeared useful for management of cancer pain in humans.[4] More recently, high doses of intrathecal meperidine have been used as a sole anesthesic for urologic surgery and surgery of the lower limbs,[5,6] combining two advantages. First, in the operative period, it induces a motor block.[2,5,7] Second, long-lasting and effective pain relief is present both intra- and postoperatively. However intrathecal opioids can induce respiratory depression. Although this complication is more commonly observed following intrathecal administration of hydrophilic drugs, such as morphine, rather than after lipophilic agents injection, such as meperidine or fentanyl,[8] the fact that the mechanisms of this depression remain unclear[9] limits the use of such a technique. It has been suggested[10] that three mechanisms might account for the access of the opioid to brain stem respiratory centers: 1) rostral movement in the CSF, 2) vascular absorption followed by an intraventricular choroid plexus secretion, and 3) movement up Batson's perivertebral plexus.[11] The relative role of each of those mechanisms has not been precisely investigated mainly for ethical considerations. Whereas plasma kinetics following intrathecal injection of meperidine are now well documented,[12,13] CSF kinetics following intrathecal administration have not been extensively studied and data on its lumbar absorption only are available.[14,15]

This study was thus designed to compare plasma and ventricular CSF pharmacokinetics of meperidine after lumbar intrathecal injection of 1 mg · kg^{-1} in humans to further enhance understanding of the mechanisms leading to both respiratory depression and pain relief.

Materials and Methods

The study was approved by the Ethics Committee of the Medical Faculty of Bordeaux and the informed consent of the patient's guardian was obtained.

PATIENT SELECTION

Since 1984, intracranial pressure monitoring by means of a ventricular catheter has been carried out in 256 patients referred to the trauma center of the Teaching Hospital of Bordeaux and suffering from severe head injury. Of this group, five patients required surgery for lower limb injuries between the 5th and the 10th day following injury and once the clinical status and the intracranial pressure allowed such surgery. The operation was performed just before removal of both the intraventricular and arterial catheters. In order to avoid a change in level of consciousness, spinal anesthesia was used. Patient data on the day of surgery are listed in table 1.

ANESTHETIC TECHNIQUE

Neuroprotective medication was stopped at least 48 h prior to operation. At that time, the trachea of each patient was intubated, and the patients spontaneously breathed a gas mixture with an FI_{O_2} sufficient to maintain normal arterial oxygenation. Spinal anesthesia was performed at L3/4 interspace without preanesthetic medication and after an intravenous infusion of 300–500 ml of colloid solution. Two ml of CSF were used for bacteriological and biochemical controls. One mg · kg^{-1} of meperidine (2 ml vial containing 100 mg, density = 1.014 g · ml^{-1}) was then injected without barbotage, over ap-

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TABLE 1. Patient Data on the Surgical Day

Patient	Age/Sex (year) (M/F)	Body Weight/Temp. (kg) (°C)	ICP mmHg	GCS	Delay from Trauma (day)	Nature of Brain Trauma	Surgery
1	19 M	75 38°2	8	7	8	Contusion	Burn Excision
2	18 F	56 38°5	8	8	10	Contusion	Pinning of Femur
3	28 M	76 38°4	12	6	7	Brain Swelling	Pinning of Femur
4	63 M	74 37°9	5	6	4	Brain Anoxia	Wound Dressing
5	24 M	66 38°4	8	8	7	Contusion	Pinning of Metatarsal Bone

ICP = intracranial pressure; GCS = Glasgow Coma Scale.

proximately 30 s through a 25 G needle and with the patient in the lateral decubitus position. Patients were then positioned supine with trunk and head tilted up 15°. Perioperative hydration was carried out with lactated Ringer solution (15 $ml \cdot kg^{-1}$). Blood replacement was not required as blood loss was slight. Intra- and postoperative monitoring included ECG, blood pressure, and end-tidal CO_2 which were continued throughout a 24 h postsurgery period, during which time the trunk was maintained in a constant position while the legs were slightly elevated.

PHARMACOKINETICS

Blood samples were withdrawn into heparinized tubes *via* the arterial catheter every 2 h up to the 16th hour. Additional determinations were obtained every 15 min during the first hour and at the end of the second hour. Plasma was separated by centrifugation, and stored at −20° C. Meperidine was assayed by gas chromatography with azote phosphorus flame ionization detection (NPFID). Plasma (or CSF) were alkalinized, extracted, and centrifuged. An aliquot of the organic layer was applied to an OV 1 column. The detection limit of the method was 3 $ng \cdot ml^{-1}$ and the coefficient of variation was 2.5%. Two ml of ventricular CSF samples were taken from the indwelling catheter (dead space 0.2 ml) at the end of the first and second hour and then every 2 h up to the 16th hour after administration. The following pharmacokinetic parameters were computed: Cmax ($ng \cdot ml^{-1}$)—observed peak plasma concentration; Tmax (h)—time to Cmax (observed value); and t1/2el—elimination half-life ($0.693 \cdot \beta^{-1}$) where β is the slope of the terminal phase of the linear relationship determined by means of the least squares method between log values of actual concentration and time.

The results are presented as mean ± SEM.

Results

In all patients, the clinical course was uneventful over the observation period. No respiratory depression occurred during either the operative period or postoperative period as reflected by abnormal end-tidal CO_2 and Pa_{CO_2} (data not shown). Plasma and ventricular CSF concentration of meperidine *versus* time are shown in table 2.

TABLE 2. Plasma and Ventricular CSF Data

Patient		Time (h) .25	.50	.75	1	2	4	6	8	10	12	14	16
1	Plasma	67	103	106	111	103	99	56	38	25.6	17	11	8
	VCSF				25	515	49.7	35	25	15	7.2	5.7	3
	Ratio				0.22	0.5	0.5	0.62	0.65	0.58	0.42	0.51	0.37
2	Plasma	714	326	491	235	186	73	51	27	9	ND	ND	ND
	VCSF				45.8	30.8	13.7	6.3	3.2	ND	ND	ND	ND
	Ratio				0.19	0.16	0.18	0.12	0.11				
3	Plasma	170	180	195	180	170	140	110	71	52	37	25	20
	VCSF				48	44	23	11	7.7	6	ND	ND	ND
	Ratio				0.26	0.26	0.16	0.1	0.1	0.1			
4	Plasma	M	M	M	M	310	192	129	70	39	18	14	6
	VCSF				124	120	64	43	26	15.5	9.7	6.4	3.3
	Ratio					0.38	0.33	0.34	0.37	0.39	0.53	0.45	0.55
5	Plasma	87.5	139	236	346	320	206	179	122	87.5	65	37	23
	VCSF		10.7		26.7	53	49.5	44.2	35	21.7	13	8	5
	Ratio				0.07	0.16	0.24	0.24	0.28	0.25	0.2	0.21	0.21

Individual concentrations ($ng \cdot ml^{-1}$) of meperidine in the plasma and ventricular CSF according the duration of the postoperative period. M = value missing; ND = value not detectable.

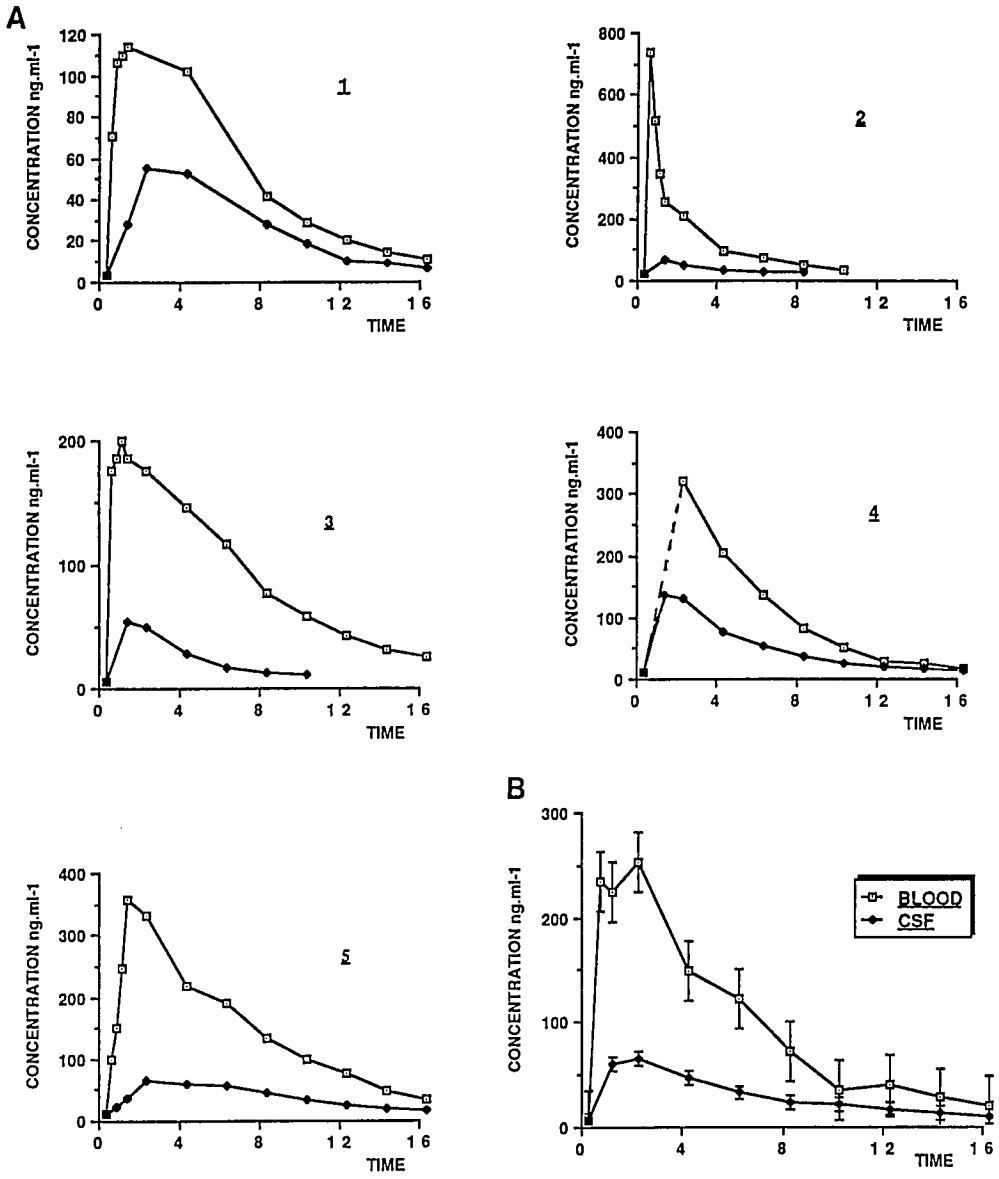

FIG. 1. Relationship between meperidine concentration in plasma (- ◇ - ◇ -) as well as in the ventricular CSF (- ■ - ■ -) and time after injection. *A.* Individual data. *B.* Mean values for the group.

PLASMA KINETICS

Figure 1 shows the concentrations of meperidine in the plasma and in the ventricular CSF in each patient (fig. 1A). Mean results for the group are also presented (fig. 1B). Absorption from lumbar CSF was rapid, and the peak plasma concentration was observed at 45 ± 17 min after administration. Unfortunately, early samples for patient 4 were omitted and thus Cmax and Tmax could not be determined for this patient. Moreover, there was considerable interindividual variability in the extent of absorption (Cmax ranging from 111 to 714 ng · ml^{-1}). Table 3 shows individual pharmacokinetic data.

TABLE 3. Plasma Kinetics Data

Patient	1	2	3	4	5	Mean	SEM
C max (ng · ml^{-1})	111	714	195	—	346	341	133
T max (h)	1	0.25	0.75	—	1	0.45	0.28
T1/2 el (h)	3.33	1.97	4.16	2.49	3.73	3.14	0.4

Individual plasma kinetics data and mean values: elimination half-life (T1/2 el), maximum concentration and time to reach maximum concentration (Cmax, Tmax). Note that Cmax and Tmax in patient 4 were not determined (see text and table 2) and thus mean ± SEM values are computed for the remaining four patients.

TABLE 4. Ventricular CSF Kinetics Data

Patient	1	2	3	4	5	Mean	SEM
C max ($ng \cdot ml^{-1}$)	51.5	45.8	48	124	53	64.5	14.9
T max (h)	2	1	1	1	2	1.4	0.24
T 1/2 el (h)	2.67	1.77	2.69	2.75	3.72	2.72	0.3

Individual ventricular CSF kinetics data. Headings are similar to those in table 3.

VENTRICULAR CSF KINETICS

As shown in figure 1, meperidine was detected in the first ventricular CSF sample withdrawn 1 h after lumbar administration. In patient 2, 3, and 4, values given as Tmax are not actual Tmax but, rather, maximal values determined according to the protocol. The peak concentration was observed 1.4 ± 0.24 h after injection. Table 4 summarizes individual pharmacokinetic data and mean values for the group.

PLASMA AND VENTRICULAR CSF PHARMACOKINETICS COMPARISON

In figure 2 are plotted ventricular CSF-plasma concentration ratios *versus* times. The linear regression equation was ventricular CSF/blood = 0.16 + 0.017 time, showing that the ratio increased with time (r = 0.82) from a value of 0.18 ± 0.04 at the first hour to 0.38 ± 0.1 at 16th hour.

Discussion

These results show that meperidine is detectable in ventricular CSF at the first hour after intrathecal administration, the concentration being, however, 1/3 to 1/5 that found in the plasma.

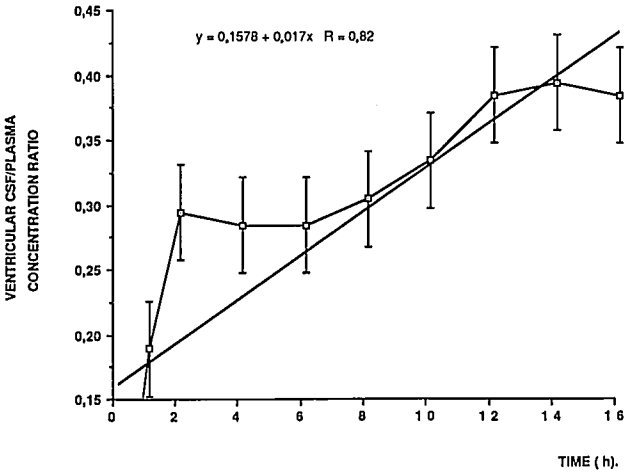

FIG. 2. Relationship between ventricular CSF-plasma concentration ratio of meperidine and time after injection. Data are given as mean. Vertical bars indicate SEM. The linear regression is also shown.

It could be argued that these results obtained in patients with severe head injury might not be relevant to patients without cranial pathology. However, the clinical course estimated from the Glasgow coma scale was favorable in all patients. Moreover, the results of the sequential CT scans, the rapid decrease of intracranial pressure to normal value, and the biochemical features of the CSF suggest that the intracranial pressure-volume relationship of these patients was within a normal range on the day of the operation.[16] Furthermore, the same investigators found that absorption and CSF production were only slightly altered in patients suffering from similar injury and at this same interval after injury.[17] Additionally, physiologic studies in animals have shown that a variation in the hydrostatic pressure ranging from −10 to 30 cm water had no significant effect on the rate at which CSF is produced.[18] Thus, one can assume that the results of the present study are not relevant to only head-injured patients.

It is unlikely that the removal of samples of ventricular CSF altered the movement of CSF within the ventricular and spinal system and, thus, the rate of spread of meperidine. As discussed above, it is reasonable to assume that CSF production in these patients was within a normal range (*i.e.*, 0.3–0.4 $ml \cdot min^{-1}$ [19]). Consequently, throughout the study, about 300 ml of CSF were produced, whereas only ten samples of 2 ml were withdrawn. This represents about 0.6% of the CSF produced, which would not significantly change CSF dynamics.[20] Similarly, the bulk flow of meperidine depends on the position. In our study, a 15° head-up position was selected, as it is the one currently recommended for spinal anesthesia with opioids.[21] We doubt that such a position played a major role in the observed results, although its effect would require further investigation.

The absorption of meperidine into plasma observed in this study is in good agreement with data previously reported in the literature. This lipophilic drug is rapidly and widely absorbed.[22] However, a considerable interindividual variation was noted: a sevenfold variation in the present study, while a 12-fold variation was reported after epidural injection.[14] It should be noted that, in this study, plasma concentrations were higher than those reported by others using the same intrathecal dose.[12,13] The fact that our patients had a rectal temperature higher than 38° C could have increased vascular absorbtion *via*

an increase of the local blood flow. However this effect of temperature on vascular absorption is certainly slight, as cardiac output only increases about 400 ml · min^{-1} for this level of hyperpyrexia.[23] Moreover, Rowell[24] has shown that medular blood flow is protected from changes in the cardiac output. Age and gender are important factors involved in vascular absorption and in the amount of lipid present. Variations in these factors might account for the differences observed among those studies.[25,26] Incidentally, it should be noted that the only woman, the youngest in the group (table 1), had both the highest temperature at operation and the highest plasma level of meperidine (714 ng · ml^{-1}, 15 min after injection). Apart from this value, all the other values were below levels (400–500 ng · ml^{-1}) required for systemic analgesia.[27,28]

The fact that meperidine is a lipophilic narcotic explains both the fact that spinal cord receptors are rapidly occupied permitting such surgery as well as the rapid systemic uptake. It is thus not surprising that elimination half-life values found in our group are in agreement with the pharmacokinetic characteristics of meperidine after both intravascular and intramuscular administration.[28,29]

We observed that meperidine appears in ventricular CSF soon after lumbar administration, suggesting at least initially diffusion from blood rather than movement *via* CSF. It was reported that the bulk movement of CSF from the lumbar space into the cisterna magna occurred within a 3–6-h interval.[30,31] That initial meperidine concentration in CSF was due to diffusion from blood would be further supported when comparing the time course of meperidine concentration in ventricular CSF and blood. Both curves were similar in each patient and Tmax was reached in CSF after it was reached in the blood. Thus, the blood-brain barrier does not appear to play a major role in meperidine diffusion between CSF and blood. It has already been shown that diffusion occurs in choroid plexus[32,33] and several investigators have demonstrated that passive diffusion was the source of the opioid movement from blood to lumbar CSF.[34–36] As the free fraction of meperidine in blood ranges from 20 to 40%[28] and, as suggested recently, 60% of the total,[37] the meperidine concentration in the CSF we measured in our patients may well reflect diffusion of free drug component from blood into the ventricular CSF. Additionally, our results confirm those of Boreus *et al.*[34] These authors reported that, when injected intramuscularly, meperidine appeared rapidly in lumbar CSF. These results were interpreted as being in agreement with the concept that the concentration of a drug in the lumbar CSF is correlated with that in the blood at equilibrium. The fact that the ventricular CSF-plasma concentration ratio was correlated with time suggests that a steady state was not achieved in the present study, unlike the study by Boreus *et al.* Several mechanisms might account for this fact: 1) the route of meperidine administration was different in the two studies, 2) it could also be argued that ventricular CSF-plasma concentration ratio increased with time (fig. 2) partially because of an upward migration from the lumbar injection site,[31] and 3) Hug[38] has shown that active transport by choroid plexus is able to concentrate narcotics *in vitro.*

Further studies are required in order to confirm these hypotheses. This also highlights the difficulties found in comparing pharmacokinetics data when compartment theory cannot be applied with confidence.[8]

From a practical point of view, these results suggest that the levels of meperidine in the ventricular CSF are directly related to those in the plasma and consequently to the magnitude of absorption. Although these levels are, in most cases, not sufficient to induce systemic analgesia,[27,28] they may be responsible for the generalized side effects of the drug, *i.e.,* pruritis, drowsiness, vomiting.[39] The respiratory depression may derive from the high plasma level. It has been reported that when meperidine is administrated intravenously, respiratory depression occurs following circulating levels around 500 ng · ml^{-1} [40] to 800 ng · ml^{-1},[29] depending on the injection technique. This would indicate that the safety margin of the dose used in this study (1 mg · kg^{-1}) is low, provided that the relationship between respiratory depression and blood concentration is identical whatever the route of administration. Owing to the wide interindividual variation in plasma pharmacokinetics of this agent, the benefit-risk ratio of this technique is not very high. Particular attention is thus needed during the first hours after both intrathecal or epidural anesthesia, especially if reinjections are required.[41–43]

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